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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant	:	Kameron W. Maxwell et al.
App. No	:	10/675,225
Filed	:	September 29, 2003
For	:	NITROXIDE RADIOPROTECTOR FORMULATIONS AND METHODS OF USE
Examiner	:	James William Rogers
Art Unit	:	1618

CORRECTED APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Corrected Appeal Brief is submitted in response to a Notification of Non-compliant Appeal Brief mailed November 7, 2007, in which the Examiner noted that the brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters. The Appeal Brief now fully complies with 37 C.F.R. § 41.37.

Should any additional fees be necessary, please charge them to our Deposit Account No. 11-1410.

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I. REAL PARTY IN INTEREST

Pursuant to 37 C.F.R. § 1.192, Appellants hereby notify the Board of Patent Appeals and Interferences that the real party in interest is the assignee of this application: Mitos Pharmaceuticals, Inc., 3 San Joaquin Plaza, Suite 200, Newport Beach, CA, 22660.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

III. STATUS OF CLAIMS

The above-identified application was filed with 25 claims. Claims 1-25 were rejected by the Examiner in an Office Action mailed April 11, 2006. Subsequently, Claims 11, 13, 16, 24, and 25 were amended and Claim 18 was canceled. Claims 1-17 and 19-25 were finally rejected in an Office Action mailed September 15, 2006. Subsequent to that Office Action, Claim 24 was amended. The amendment to Claim 24 was not entered for purposes of appeal by the Examiner in an Advisory Action mailed February 16, 2007, in which the Examiner indicated that Claims 1-17 and 19-25 remained rejected. Accordingly, Claims 1-17 and 19-25 are the subject of this appeal. The claims are attached hereto as Section VIII.

IV. STATUS OF AMENDMENTS

In the Advisory Action mailed February 16, 2007, the Examiner indicated that the amendments filed subsequent to the final rejection of the claims would not be entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to radioprotective nitroxide compositions used during radiation treatments. Prior art compositions caused topical burning during radiation treatment; use of the claimed compositions allows the amelioration or avoidance of topical burning resulting from the bolus effect. The composition may be in the form of a low-residue gel or low-residue thickened liquid. The nitroxide-containing composition may be applied to skin, and the solvent therein allowed to evaporate before applying radiation. *See, e.g.*, specification at ¶¶[0060] – [0065].

Independent Claim 1 is directed to a pharmaceutical composition for use in ameliorating an effect of radiotherapy on skin, mucous membranes, or hair follicles. The claimed composition comprises a solvent and an effective prophylactic or therapeutic amount of a

nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel. *See, e.g.*, specification at ¶¶[0077] and [0080].

Independent Claim 13 is directed to a pharmaceutical composition for use in ameliorating an effect of radiotherapy to skin or mucous membranes. The claimed composition comprises a solvent and an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel or low-residue thickened liquid that does not leave an amount of residue sufficient to enhance burning to the skin or mucous membranes when radiotherapy is applied. *See, e.g.*, specification at ¶¶[0079]- [0080].

Independent Claim 15 is directed to a pharmaceutical composition for use in treating alopecia. The claimed composition comprises solvent and an effective prophylactic or therapeutic amount of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel. *See, e.g.*, specification at ¶[0017].

Independent Claim 16 is directed to a method for treating a patient. The claimed method comprises topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat harmful side effects caused by radiotherapy, wherein the nitroxide radioprotector is in solution in a solvent, and the solution is in the form of a low-residue gel or a low-residue thickened liquid. *See, e.g.*, specification at ¶[0102]-[0105].

Independent Claim 24 is directed to a method for treating a patient. The claimed method comprises topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent; evaporating solvent; and applying radiotherapy to the patient. *See, e.g.*, specification at ¶[0019], and Examples I and II.

Independent Claim 25 is directed to a method for treating a patient. The claimed method comprises topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent, has a sufficient viscosity such that it is retained in place on the patient, and the

solution is in the form of a low-residue gel or a low-residue thickened liquid; and applying radiotherapy to said patient. *See, e.g.*, specification at ¶[0020], and Examples I and II.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Examiner has rejected Claims 1-2, 6-10, 12-18, and 20-25 under 35 U.S.C. § 102(b) as being unpatentable over Mitchell et al., United States Patent No. 5,462,946, and has rejected Claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Mitchell et al., in view of Golz-Berner et al., International Patent Application Publication No. WO 99/66881 (using United States Patent No. 6,426,080 as an equivalent).

VII. ARGUMENT

The Examiner has maintained his rejection of Claims 1-2, 6-10, 12-18, and 20-25 under 35 U.S.C. § 102(b) as being unpatentable over Mitchell '946, and has maintained his rejection of Claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Mitchell '946, in view of Golz-Berner '080. The Examiner maintained the rejection based on allegations that:

(A) although Mitchell's disclosed topical formulations are limited to liquids, ointments, lotions, or creams, Mitchell nevertheless discloses both "gel" and "thickened liquid" formulations;

(B) although Appellants' originally-filed specification specifically distinguished Mitchell's topical "ointment, lotion, or cream" formulations as leaving a significant residue on the skin, Mitchell nevertheless discloses a "low residue" formulation; and

(C) one of skill in the art would employ certain solvents disclosed in Golz-Berner to produce low-residue formulations of the active ingredient disclosed in Mitchell, even though Golz-Berner indicates that other ingredients are to be included in those compositions and the presence of those ingredients would leave a significant residue on the skin.

Each of these allegations is addressed below.

A. Claims 1-2, 6-10, 12-18, 20-23, and 25 Are Not Anticipated By Mitchell '946

1. Mitchell Discloses Neither A "Thickened Liquid" or a "Gel" Formulation

In order to establish a *prima facie* case of anticipation, the Examiner is required to demonstrate that all of the limitations of the claims are present in a single prior art reference. *See* M.P.E.P. § 2131. The Examiner has failed to do this. Indeed, the Examiner has essentially

ignored the "thickened liquid" and "gel" limitations that are present in almost all of the pending claims.

a. Applicant's Claims Require A "Thickened Liquid" or a "Gel" Formulation, Which Are Described In Applicant's Specification

Independent composition Claims 1 and 15 require that the pharmaceutical composition be "in the form of a low-residue gel." Independent composition Claim 13 requires that the pharmaceutical composition be "in the form of a low-residue gel or low-residue thickened liquid." Independent method Claims 16 and 25 require that the solution be "in the form of a low-residue gel or low-residue thickened liquid." Thus all of these claims, and their dependent claims, require that the claimed composition, or composition employed in the claimed method, be in the form either of a "gel" or a "thickened liquid." For greater clarity, Applicants further described both of these forms in the specification.

A "gel" is a "semisolid system of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Generally, if left undisturbed for some time, gels may be in a semisolid or gelatinous state." Specification at ¶ [0091]. Gels will also "typically comprise a major amount of a liquid phase and a minor amount of a thickening or gelling agent." Specification at ¶ [0064].

According to Applicants' specification, a thickened liquid may be obtained by adding polymers to a nitroxide-containing solution to achieve a dynamic viscosity of 20-100,000 or more centipoise. Specification at ¶¶ [0099], [0101].

Furthermore, Applicants clearly distinguished both the gel and thickened liquid formulations from other formulations, such as "creams, lotions, shampoos, cream rinses, and ointments," which "are unsuitable for administration shortly before the actual delivery of radiotherapy to the patient. Indeed, these product forms leave residues that can result in topical burning, including severe burns, when radiation is administered." Specification at ¶ [0009].

b. The Examiner Ignored Both The "Gel" and "Thickened Liquid" Limitations and Applicant's Relevant Disclosure

It is axiomatic that, in order for a printed publication to anticipate a claim, that reference must disclose elements corresponding to each limitation of the claim. *Verdegaal Bros. v. Union*

Oil Co. of Calif., 814 F.2d 628, 631 (Fed. Cir. 1987). The Examiner was confronted with claims that clearly were limited to "gel" or "thickened liquid" formulations, and had the benefit of clear guidance as to the meaning of those limitations and how they could be distinguished from other formulations. The Examiner's citation of Mitchell '946 as an anticipating reference is, therefore, only proper if it discloses a pharmaceutical composition that is in the form of a "gel" or a "thickened liquid." It does not. This rejection is unjustified, and under these circumstances is frankly incomprehensible to Applicants.

The Examiner began his substantive prosecution of this case by identifying Mitchell's disclosure of a topical "ointment, lotion, or cream" as "satisfying the claim for a gel or thickened liquid." Office Action mailed April 11, 2006 at 2. Applicants responded by directing the Examiner's attention to the relevant portions of their specification, which indicated that Mitchell's topical formulations were in fact not gels or thickened liquids, and that ointments, lotions, or creams such as those disclosed in Mitchell would cause burning on delivery of radiotherapy, avoidance of which was a primary motivation to create the claimed invention. Response of August 11, 2006 at 7. The Mitchell formulations clearly did not fall within the literal scope of the "gel" or "thickened liquid" limitations. The Mitchell formulations' unsuitableness for the claimed purpose reinforced this conclusion. Applicant therefore requested that the Examiner recognize that Mitchell failed to disclose "gel" or "thickened liquid" formulations, and withdraw the rejection under Section 102. Id. at 9.

The Examiner responded by noting Applicants' assertion that Mitchell did not disclose formulations corresponding to these limitations, but stating that "the relevance of this assertion is unclear." Office Action mailed September 15, 2006 at 2. In so doing, the Examiner implicitly denied the "gel" and "thickened liquid" limitations any patentable weight, which was clearly improper. Evidently, however, the Examiner did recognize that his first rejection was somehow inadequate, because he went on to cite other Mitchell formulations, specifically "an aerosol drop or spray," which he maintained would also "satisfy the limitation of a low residue gel or low residue thickened liquid." *Id.* at 3. Unlike the ointments, lotions, and creams originally cited by the Examiner, the aerosols, drops, and sprays of Mitchell are not topical formulations designed to protect the skin, but are rather for inhalation, placement in the eyes, or application to plants.

Mitchell '946 at col. 2, line 63 – col. 3, line 30. Furthermore, none of these forms meets either the "gel" or "thickened liquid" limitations.

Mitchell '946 does contain a brief reference to a topical "liquid" formulation. *See* Mitchell '946 at col. 5, line 19. However, there is simply no disclosure of a "thickened liquid," and that is what is claimed. Furthermore, Applicant's specification clearly indicates that "liquids" are to be distinguished from "thickened liquids," since it discusses them as separate alternatives. *See* specification at ¶¶ [0062], [0069], [0079], [0098]-[0101]. Mitchell's brief mention of a topical "liquid" formulation is therefore insufficient to meet the "thickened liquid" limitation.

2. Applicant's Claims Also Require A "Low-Residue" Formulation, Which Is Not Disclosed By Mitchell

Claims 1-2, 6-10, 12-18, 20-23, and 25 also require that the formulation be "low-residue." The Examiner appears to have ignored this limitation of the pending claims as well, and has identified no disclosure in Mitchell that corresponds to this limitation. Indeed, Mitchell appears to have been unaware of the problem of topical burning caused by such residues.

As the present specification makes clear, prior art creams, lotions, shampoos, cream rinses, and ointments such as those disclosed in Mitchell leave residues on the skin that can result in severe burning when applied shortly before the administration of radiotherapy. *See* specification at ¶ [0073]. The avoidance of the problem of residue-induced burning by the described and claimed low-residue formulations was recognized by the Applicant. *See* specification at ¶ [0064]. Indeed, "low-residue" is defined in terms of such burning in the specification: "[a]s used herein, 'low-residue' refers to formulations that can be applied to a patient, shortly before undergoing radiotherapy, without leaving a residue capable of enhancing a bolus effect upon delivering radiotherapy to the treated area." Specification at ¶ [0084].

The Examiner has consistently failed to identify any disclosure of a "low-residue" formulation in Mitchell. Nor has he identified any motivation to modify the disclosures of Mitchell to make a low-residue formulation. Instead, he has simply pointed to the disclosure in Mitchell of topical ointment, cream or lotion formulations (or aerosol drop or spray formulations) as somehow satisfying the "low-residue" limitation. *See, e.g.,* Office Action mailed April 11, 2006 at 2; Office Action mailed September 15, 2006 at 3; Advisory Action at 2.

Yet these are the same formulations specifically distinguished in the present specification as not being "low-residue" formulations. *See* specification at ¶ [0009] (specifically describing prior art including Mitchell as "limit[ing] the topical use of Tempol to formulations selected from creams, lotions, shampoos, cream rinses, and ointments" that "leave residues that can result in topical burning, including severe burns, when radiation is administered."). Applicant states that Mitchell's formulations are not low-residue; in effect, the Examiner tells the Applicant that he is wrong. The Examiner has no apparent basis to do so.

Applicant did direct the Examiner's attention to the need for a "low-residue" disclosure during prosecution. In response to the Examiner's final rejection over Mitchell, Applicant provided the Examiner with further evidence of standard definitions of terms such as "ointment" and "cream." Amendment and Response filed January 16, 2007 at 6-7. Applicant noted that the U.S. Food and Drug Administration's Center for Drug Evaluation and Research Data Standards Manual defines an "ointment" as "[a] semisolid dosage form, usually containing <20% water and volatiles and >50% hydrocarbons, waxes, or polyols as the vehicle." Furthermore, it defines a "cream" as "an emulsion, semisolid dosage form, usually containing > 20% water and volatiles and/or < 50% hydrocarbons, waxes, or polyols as the vehicle." As Applicant argued, dosage forms containing such significant amounts of residue-producing substances will not be "low-residue." Neither are "lotions" limited to low-residue forms: they are defined by the FDA simply as "[a]n emulsion, liquid dosage form." Indeed, as Applicant noted, guidelines to patients undergoing radiation therapy generally counsel specifically against the use of lotions on the treated area during therapy.

Accordingly, the Examiner has filed to identify a disclosure in Mitchell '946 that corresponds to the "low-residue" limitation of Claims 1-2, 6-10, 12-18, 20-23, and 25, and the rejection of those claims over Mitchell must fail on this ground as well.

3. The Examiner's Final Anticipation Rationale Does Not Apply To Claims 1-12 and 15

In response to Applicant's January 16, 2007 response, the Examiner issued an Advisory Action. In explaining his rejection over Mitchell, the Examiner made a candid and rather startling admission relevant to his examination of these claims. Specifically, he indicates that he focused on the "thickened liquid" limitation to the exclusion of the "gel" limitation:

> Thickened liquid or gel was interpreted in the broadest reasonable way by the examiner therefore the recitation of "thickened" is not considered to be very limiting. The examiner searched thickened liquid or gel to mean <u>any composition</u> that contained a solvent or a solution in which the solvent/solution was more viscous or thickened after addition of the ingredients, for example to make a cake one would use milk and flour, upon mixing milk with flour the batter is more thickened or viscous than just milk alone, the limitation was interpreted in a similar manner. Since an ointment, cream or lotion is thicker or more viscous than a solvent or solution the limitation is considered met.

Advisory Action of February 16, 2007 at 2 (emphasis added).

The "thickened liquid" limitation is, however, entirely absent from Claims 1-12 and 15. The Examiner's reasoning does not apply to those claims. The Examiner here maintains that any sort of composition containing a thickened solution meets the "gel" limitation, including the ointments, creams, and lotions disclosed in Mitchell. As a matter of standard usage in the art, this is clearly wrong. Each of these terms has a distinct meaning, and ointments, creams, and lotions are not gels. *See* Amendment and Response mailed January 16, 2007 at 6-7. The Examiner's conclusion that an ointment, cream, or lotion satisfies the "gel" limitation is incorrect. Accordingly, based on the Examiner's own searching and examination rationale, Claims 1-12 and 15, at least, should be allowable over Mitchell.

Because the Examiner has failed to identify a disclosure in Mitchell of a topical composition in the form of a "gel" or "thickened liquid," or a "low-residue" composition, he has failed to establish a prima facie case of anticipation of Claims 1-2, 6-10, 12-18, 20-23, and 25 by Mitchell, and Applicant requests that this rejection be reversed.

B. <u>Claim 24 Is Not Anticipated By Mitchell '946</u>

Pending Claim 24 recites the steps of "evaporating solvent; and applying radiotherapy to said patient." In rejecting this claim as anticipated by Mitchell, the Examiner stated that "applying the composition topically to prevent harmful effects of radiotherapy is taught by Mitchell (*see* col. 2, lines 53-58) and evaporating solvent after applying topically is inherent since the solvents listed are volatile (methanol) and would eventually evaporate when applied to a person's skin." Office Action mailed April 11, 2006 at 3.

To anticipate Claim 24, evaporation of the solvent in the formulation must take place before the radiotherapy is applied to the patient. Mitchell does not disclose the timing of the application of the topical formulations with respect to the application of ionizing radiation. Furthermore, as recognized by the Examiner, Mitchell is silent as to the specific solvents to be employed. *See* Office Action mailed April 11, 2006 at 2. It is possible that, if applied well in advance of the application of ionizing radiation, the undisclosed solvent in the "ointment, lotion, or cream" formulation of Mitchell will evaporate before ionizing radiation is applied. The Examiner apparently recognized that he needed to establish that the solvent would always evaporate before the application of radiotherapy, because he later based his inherency rationale on a speculation that the solvent would "evaporate almost immediately." Office Action mailed September 15, 2006 at 3.

However, "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); *see also* M.P.E.P. § 2112(IV). Rather, "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F.3d at 745. Despite the Examiner's speculation, the precise timing of the evaporation of an undisclosed solvent from a composition applied to the skin is simply not ascertainable. Particularly where the timing of application is not disclosed, a disclosure of the evaporation of that solvent before the application of later radiotherapy is not "necessarily present."

Because Mitchell does not disclose either the solvent to be employed or the timing of the application of the topical formulation, a disclosure of evaporation of the solvent before the application of ionizing radiation is not "necessarily present" in Mitchell. For this reason, the Mitchell disclosure does not inherently anticipate Claim 24, and Applicant requests that this rejection be reversed.

C. Claims 1-17 and 19-25 Are Not Obvious In View Of Mitchell '946 and Golz-Berner '080

The Examiner has rejected Claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Mitchell '946, in view of Golz-Berner et al., PCT Publication No. WO 99/66881. Claim 18

was canceled in the Response filed on August 15, 2006. Because the Examiner has failed to make out a *prima* facie case of obviousness over this combination of references, Claims 1-17 and 19-25 are not obvious in view of this combination of references.

1. The Examiner Has Not Established A *Prima Facie* Case Of Obviousness Of Claims 1-17 and 19-25

a. Neither Mitchell Nor Golz-Berner Discloses a "Low-Residue" Formulation

The topical formulations of the present application are designed to leave little residue on the skin after a short period of time, in order to ameliorate or avoid the problem of burning caused by radiotherapy. One of skill in the art would not produce a "low-residue" formulation even by combining the teachings of Mitchell and Golz-Berner.

As noted above, Mitchell discloses the use of a topical radioprotective formulation in the form of an ointment, cream, lotion, or liquid. As discussed above, none of these formulations satisfy the "low-residue" limitations of the claims.

The Examiner relies on Golz-Berner for "its disclosure of cosmetic active substances to protect the skin and the use of solvents, carriers, and hydrogels." Office Action mailed September 15, 2006 at 5. The Examiner states that "it would have been obvious to modify the solvents and carriers of Golz-Berner with the composition of Mitchell, especially since they are related to the same field of endeavor." Advisory Action of February 16, 2007 at 2. In essence, the Examiner takes Golz-Berner's disclosure of the use of water and certain glycols in cosmetic preparations to be the equivalent of the disclosure of a low-residue gel. It is not.

Like all references cited in an obviousness rejection, Golz-Berner must be considered in its entirety, including portions that would lead away from the claimed invention. *See W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-51 (Fed. Cir. 1983); M.P.E.P. §2141.02(VI). When Golz-Berner is considered in its entirety, its disclosure would not lead one of skill in the art to a low-residue gel or low-residue thickened liquid.

Applicant's specification makes clear that the low-residue formulations can be achieved by including only a very minor amount of a gelling agent, which remains behind after evaporation of the solvent together with the active ingredient. *See* specification at ¶ [0064].

Thus "98%, 99% or more of the carrier for the drug can disappear prior to radiotherapy, greatly reducing or eliminating burning due to the bolus effect." *Id.*

In contrast, Golz-Berner is concerned with the preparation of cosmetic preparations, with one stated objective of the invention being "to provide a preparation of active substances that keeps its radical protection potential over a long period of time." Golz-Berner at col. 1, lines 52-54. In its broadest disclosure, Golz-Berner teaches that the preparation achieves an incorporation of the active ingredients in an "association complex" containing not only the hydrogel components identified by the Examiner, but also a significant fraction of phospholipids (up to 30% by weight). *See* Golz-Berner at col. 2, lines 11-12; col. 3, lines 37-42. One of skill in the art, on reviewing the Golz-Berner reference for disclosure of how to prepare a topical radioprotective formulation, would also incorporate these phospholipids into the formulation to form a similar association complex with the nitroxide active ingredient. The Examiner notes that Mitchell does not disclose the use of these phospholipids, *see* Advisory Action at 2, but it is after all the disclosure of Golz-Berner, not Mitchell, that the Examiner must rely on for the disclosure of how to make the low-residue gel or thickened liquid. Furthermore, one of skill in the art would obviously turn to the exemplary formulations, rather than a laundry list of possible ingredients, for guidance in producing the actual composition. The phospholipids, which have a much higher molecular weight than the disclosed solvents, would not readily evaporate, and the resulting composition would leave a residue that would cause topical burning during radiotherapy.

Furthermore, although the Examiner has treated the examples of Golz-Berner as non-limiting, see Advisory Action at 2, those examples must also be considered for what they would indicate to one of skill in the art. *See W.L. Gore*, 721 F.2d at 1550-51 (Fed. Cir. 1983). Golz-Berner discloses exemplary cosmetic compositions, the majority of which are described as "creams." Golz-Berner '080 at col. 9, line 55 – col. 11, line 28. This term coincides with Mitchell's teaching that a "cream" form should be used for the radioprotective formulation, making it more likely that one of skill would follow the specific teachings disclosed. Each of these exemplary "cream" formulations (as well as formulations described as a "sun gel" and "emulsion-based fluid") contains not only the phospholipid-containing active complex, but also a

considerable amount of glycerine. *See id.* Glycerine is highly hygroscopic and will slow the rate of evaporation of the solvents employed in the compositions. Because a significant amount of not only phospholipid but also glycerine is included in each of the exemplary formulations disclosed in Golz-Berner, topical formulations made following the teachings of Golz-Berner would not result in the "low-residue gels" or "low-residue thickened liquids" required by Claims 1, 13, 15, 16, and 25. Neither, given the presence of these ingredients, would the resulting formulations meet the requirements of Claim 24, wherein evaporation of solvent occurs before radiotherapy is applied.

As a result, even if the teachings of Golz-Berner were combined with those of Mitchell, a "low-residue" gel or thickened liquid would not result. Because a disclosure corresponding to this limitation, and the limitation of Claim 24 discussed above, are not found in the cited prior art references, a prima facie case of obviousness has not been established.

2. <u>There is No Apparent Reason to Combine the Reference Teachings</u>

The Supreme Court has recently clarified the law governing obviousness determinations. *See KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007). The Court stated that as part of the obviousness inquiry, it is necessary to "determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co.*, 127 S.Ct. at 1731; *see also Ex parte Smith,* No. 2007-1925 (Bd. Pat. App. & Interf. June 25, 2007) (precedential opinion adopting *KSR* standard in ex parte prosecution context). In this case, the Examiner has cited no such apparent reason to combine Mitchell with Golz-Berner that did not involve hindsight reconstruction of Appellants' invention.

In initially rejecting Appellants' claims over the combination of Mitchell and Golz-Berner, the Examiner observed that "the motivation to combine the two documents would be the formulation of a pharmaceutical topical gel for use as a radioprotector, the gel composition comprised of TEMPOL, solvent and polymers." Office Action mailed April 11, 2006 at 5. In other words, the Examiner's stated "reason to combine" the two documents was to recreate Appellants' invention, using their own disclosure as a blueprint. It has long been the case that such "hindsight reconstruction" is impermissible, and Appellants are not aware that recent Supreme Court precedent has changed the law in this area. Early in its existence as a court, the

Federal Circuit succinctly described hindsight reconstruction and its prohibition: "When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). Because the Examiner offered no reason to combine Mitchell and Golz-Berner other than in order to make Appellants' invention in the manner described by Appellants themselves, the combination is improper.

Furthermore, the Examiner characterizes the two references as being "from the same field of endeavor," Advisory Action at 2, but this is surely too facile. As noted above, Golz-Berner is concerned with the preparation of cosmetic preparations that contain a number of extracts from plants and insects, whereas the relevant disclosure of Mitchell is concerned with the preparation of a composition for the specific medical use of protecting against ionizing radiation such as that used in radiotherapy. One of skill in the art would be unlikely to turn to known cosmetic formulations for guidance in producing a very different medicinal formulation that would be used on skin subject to the high levels of radiation encountered in radiotherapy.

Claims 1-17 and 19-25, as presently amended, are not obvious over the cited prior art, and reversal of this rejection is respectfully requested.

CONCLUSION

In view of the arguments presented above, appellants submit that the pending claims are not obvious in view of the cited prior art combination and respectfully request that the rejections under Sections 102(b) and 103(a) be reversed, and that the application be allowed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 12-7-2007

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CLAIMS APPENDIX

1. (Original) A pharmaceutical composition for use in ameliorating an effect of radiotherapy on skin, mucous membranes, or hair follicles comprising:

a solvent; and

an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel.

2. (Original) The pharmaceutical composition of Claim 1, wherein the nitroxide radioprotector is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

3. (Original) The pharmaceutical composition of Claim 1, wherein the solvent is selected from the group consisting of water, urea, alcohols, and glycols.

4. (Original) The pharmaceutical composition of Claim 3, wherein the solvent is an alcohol selected from the group consisting of methanol, ethanol, propanol, and butanol.

5. (Original) The pharmaceutical composition of Claim 3, wherein the glycol is selected from the group consisting of ethylene glycol and propylene glycol.

6. (Original) The pharmaceutical composition of Claim 1, wherein the effect of radiotherapy is selected from the group consisting of skin conditions, mucous membrane conditions, hair follicle conditions, cytotoxicity, and polynucleic acid damage.

7. (Original) The pharmaceutical composition of Claim 6, wherein the skin condition is selected from erythema, folliculitis, fibrosis, dry desquamation, moist desquamation, hyperpigmentation, and dermatitis.

8. (Original) The pharmaceutical composition of Claim 6, wherein the mucous membrane condition is selected from oral mucositis and proctitis.

9. (Original) The pharmaceutical composition of Claim 6, wherein the hair follicle condition is alopecia.

10. (Original) The pharmaceutical composition of Claim 1, wherein the effective prophylactic or therapeutic amount of a nitroxide radioprotector is an amount from about 0.01 to about 100 mg/ml of the total composition.

11. (Previously presented) The pharmaceutical composition of Claim 1, further comprising a polymer selected from the group consisting of ethylene polymers, acrylic polymers, polyvinylpyrrolidones (PVPs), polyvinyl copolymers, cellulose polymers, natural polymers, polystyrene polymers, silicone polymers, and inorganic polymers.

12. (Original) The pharmaceutical composition of Claim 1, having a viscosity such that the nitroxide radioprotector will remain in contact with a treated area for a sufficient period of time to allow absorption of a pharmacologically effective amount into said treated area.

13. (Previously presented) A pharmaceutical composition for use in ameliorating an effect of radiotherapy to skin or mucous membranes, comprising:

a solvent; and

an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel or low-residue thickened liquid that does not leave an amount of residue sufficient to enhance burning to the skin or mucous membranes when radiotherapy is applied.

14. (Original) The pharmaceutical composition of Claim 13, wherein the nitroxide radioprotector is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

15. (Original) A pharmaceutical composition for use in preventing or treating alopecia comprising:

a solvent; and

an effective prophylactic or therapeutic amount of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel.

16. (Previously presented) A method of treating a patient, comprising topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat harmful side effects caused by radiotherapy, wherein the nitroxide radioprotector is in solution in a solvent, and the solution is in the form of a low-residue gel or a low-residue thickened liquid.

17. (Original) The method of Claim 16 wherein the nitroxide radioprotector is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

18. (Canceled)

19. (Original) The method of Claim 16, wherein the solvent is selected from the group consisting of water, urea, alcohols, and glycols.

20. (Original) The method of Claim 16 where the harmful side effect is selected from the group consisting of skin conditions, mucous membrane conditions, hair follicle conditions, cytotoxicity and polynucleic acid damage.

21. (Original) The method of Claim 20 wherein, the skin condition is selected from erythema, folliculitis, fibrosis, dry desquamation, moist desquamation, hyperpigmentation, and dermatitis.

22. (Original) The method of Claim 20 wherein, the mucous membrane condition is selected from oral mucositis and proctitis.

23. (Original) The method of Claim 20, wherein the hair follicle condition is alopecia.

24. (Previously presented) A method of treating a patient, comprising:

topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent;

evaporating solvent; and

applying radiotherapy to said patient.

25. (Previously presented) A method of treating a patient, comprising:

topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent, has a sufficient viscosity such that it is retained in place on the patient, and the solution is in the form of a low-residue gel or a low-residue thickened liquid; and

applying radiotherapy to said patient.

VIII. EVIDENCE APPENDIX

1. Specification as filed;
2. Office Action mailed April 11, 2006;
3. Response to Office Action, filed August 11, 2006;
4. Office Action mailed September 15, 2006;
5. Response to Office Action, filed January 16, 2007;
6. Advisory Action of February 16, 2007;
7. United States Patent No. 5,462,946;
8. United States Patent No. 6,426,080.

IX. RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board in any related proceedings identified above.

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